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Synthesis of Substituted Indole from 2-Aminobenzaldehyde through [1,2]-Aryl Shift

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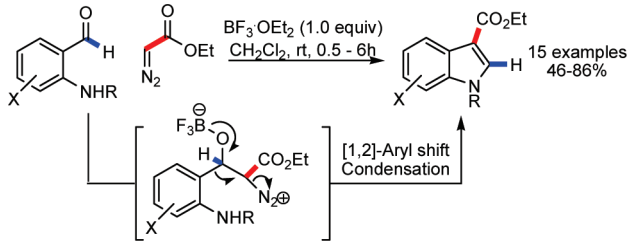
Received August 25, 2010



A mild, efficient, and simple method for the synthesis of 3-ethoxycarbonylindoles has been developed. Addition of ethyl diazoacetate (EDA) to 2-aminobenzaldehydes cleanly affords the indole core. As opposed to other common approaches for the synthesis of indole, this method displays both excellent functional group tolerance and perfect regiochemical control. This allowed the synthesis of a variety of useful indole building blocks from 2-aminobenzaldehydes derived from readily available anthranilic acids.

The indole core represents one of the ubiquitous heterocyclic scaffolds in natural products and pharmaceutical compounds.[1] The synthesis of this core has been mainly dependent on two approaches: Fisher indole-type reactions and variations of Larock indole synthesis.[2,3] The most glaring limitation of the Fisher indole-type reaction is the lack of stereochemical control during the electrophilic aromatic substitution step, resulting in a poor regiochemical control for unsymmetrical ketones.[4] For the Larock indole synthesis and its variants, the necessity for transition metals and bases can limit the substrate scope of the reaction.[5]

An interesting alternative to the indole scaffold has been reported by Pei and co-workers in which they generated indoles directly from 1-(2-aminophenyl)-2-chloroethanone and a Grignard reagent (Figure 1, top).[6] Performing an addition of an organometallic compound to this ketone affords a benzylic alkoxide. The presence of a chlorine atom at the α position promotes subsequent [1,2]-aryl migration, generating 1-(2-aminophenyl)acetone. The indole core was then rapidly formed following condensation of the aniline onto the ketone. Although interesting, this strategy is limited by the use of Grignard reagents and the availability of the requisite starting α-chloroketone.

Hossain and co-workers investigated a similar, but stepwise approach to Pei's indole synthesis.[7,8] The requisite benzylic alkoxide intermediate in this case was accessed via acid-catalyzed addition of ethyl diazoacetate (EDA) to 2-nitrobenzaldehyde (Figure 1, bottom). Subsequent [1,2]-aryl migration then furnished 2-(2-nitrophenyl)-3-oxopropanoate. The desired indole core was obtained after reduction of the nitro group and subsequent condensation of the aniline onto the aldehyde. Although the use of Grignard reagents is successfully obviated, the main downside of this stepwise procedure is that the hydrogenation step might be incompatible with various functional groups on the indole core such as nitro and bromine, groups that could allow for further functionalization. Both Pei's and Hossain's strategy are similar in that they both generate a benzylic alkoxide that undergoes [1,2]-aryl migration via displacement of a suitable leaving group at the α-position. On the other hand, the two strategies differ with regard to the nucleophile used, and while one occurs in a basic media, the other one is acid catalyzed. Here, we report a simple and straightforward addition of ethyl diazoacetate to readily available

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DOI: 10.1021/jo1016713 Published on Web 09/13/2010

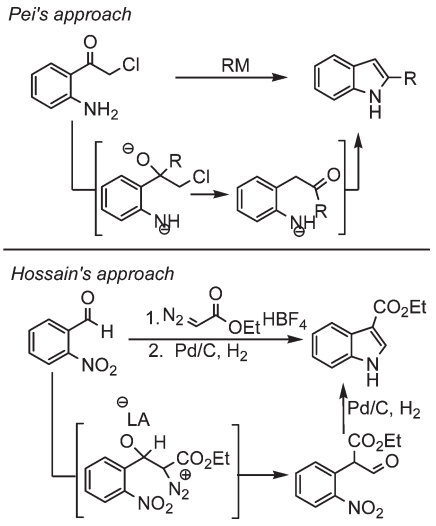
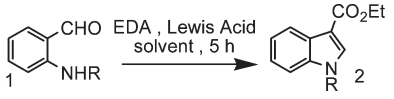


FIGURE 1. Pei's and Hossain's strategies for indole synthesis.

TABLE 1. Reaction Optimization for the Direct Synthesis of Indoles by Lewis Acid Promoted Addition of Ethyl Diazoacetate to 2-Aminobenzaldehydes[a]



entry	R	Lewis acid	solvent	yield (%)
1	H	$BF_3 \cdot OEt_2$	CH_2Cl_2	0[b,c]
2	Ts	$BF_3 \cdot OEt_2$	CH_2Cl_2	0[b]
3	Boc	$BF_3 \cdot OEt_2$	CH_2Cl_2	0[b]
4	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	56[b]
5	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	71
6	Bn	$Ti(Oi\text{-}Pr)_4$	CH_2Cl_2	0
7	Bn	$TiCl_4$	CH_2Cl_2	61
8	Bn	$SnCl_4$	CH_2Cl_2	29
9	Bn	HBF_4	CH_2Cl_2	67
10	Bn	MAD[d]	CH_2Cl_2	72
11	Bn	$BF_3 \cdot OEt_2$	THF	0
12	Bn	$BF_3 \cdot OEt_2$	DMF	0
13	Bn	$BF_3 \cdot OEt_2$	MeCN	42
14	Bn	$BF_3 \cdot OEt_2$	PhMe	60
15	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	63
16	Bn	$BF_3 \cdot OEt_2$	$ClCH_2CH_2Cl$	65
17	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	60[e]
18	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	66[f]
19	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	55[g]
20	Bn	$BF_3 \cdot OEt_2$	CH_2Cl_2	77[h]

[a]Reactions were performed in 300 μL of solvent on a 0.06 mmol scale and were stopped systematically after 5 h by dilution in acetonitrile to a total volume of 50 mL. Yields were determined by HPLC. [b]Reactions performed on 100 mg of benzaldehyde and isolated yield after flash chromatography are reported. Reagents were mixed at −78 °C and warmed to rt overnight. [c]Oligomeric mixture, see text for details. [d]Methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide). [e]0.5 equiv of Lewis acid was used. [f]1.5 equiv of Lewis acid was used. [g]2 equiv of EDA was used. [h]5 equiv of EDA was used.

2-aminobenzaldehydes to afford 3-ethoxycarbonylindoles directly under completely chemoselective conditions.

Initially, when 3 equiv of EDA was combined with 1 equiv of $BF_3 \cdot OEt_2$ and 1 equiv of 2-aminobenzaldehyde at −78 °C, a small amount of indole was observed after the reaction mixture was allowed to warm to room temperature overnight (Table 1, entry 1). Unfortunately, the desired product could not be separated from a mixture of oligomeric side products. This was not surprising since the tendency of 2-aminobenzaldehyde to form polymers is well documented.[9] To prevent the formation of oligomers, we tried to protect the aniline moiety with various groups. The reaction failed to produce any indole product with both *N*-Ts and *N*-Boc substituents (entries 2 and 3), but an isolated yield of 59% was obtained when an *N*-Bn group was used (entry 4). The use of benzyl as protecting groups for indoles is well documented and they can be removed under basic conditions,[10] acidic conditions,[11] or reductive conditions,[12] allowing the selection of the deprotection conditions that best fit the substrate.

With a suitable protecting group identified, the reaction was optimized further. For comparison purposes, all reactions were stopped after 5 h and yields were determined by HPLC. Performing the reaction at room temperature gave a 71% yield of the desired product, with only trace amounts of starting benzaldehyde **1a** and EDA remaining (entry 5).[13] The yield is not improved further when the reaction was allowed to stir overnight.

We then investigated the use of other acids to promote this reaction. No product was observed when $Ti(Oi\text{-}Pr)_4$ was used as a catalyst, presumably because it is too weak a Lewis acid (entry 6). When $TiCl_4$ was employed, only 61% of **2a** was obtained although complete consumption of EDA and the starting aldehyde **1a** was observed (entry 7). Going to $SnCl_4$ led to a further decrease in yield (29%) and numerous unknown side products were observed on the HPLC trace (entry 8). Tetrafluoroboric acid did afford product **2a** in a 67% yield, but full conversion of **1a** was not achieved although the EDA was fully consumed (entry 9). Lastly, we tried the reaction with methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD),[14] which furnished the indole product in a 72% yield (entry 10). However, since it provided no notable advantage to the simpler and cheaper $BF_3 \cdot OEt_2$, we decided to keep the latter for all subsequent reactions.

We tried changing solvent to THF or DMF, but no product was observed (entries 11 and 12). The reaction can be done in other solvents like acetonitrile, toluene, chloroform, and 1,2-dichloroethane (entries 13 to 16), but none proved to be better than dichloromethane.

We also tried to vary the amount of reactants employed in the reaction. Both increasing and reducing the amount of $BF_3 \cdot OEt_2$ used gave lower yields (entries 17 and 18). Lowering the amount of EDA to 2 equiv gave a lower yield of

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(13) Performing the reaction at a lower temperature or at various concentrations had no effect on reaction yield.

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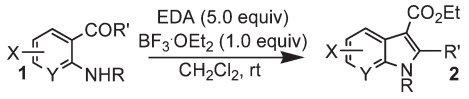
TABLE 2. Synthesis of Various Substituted Indoles[a]



Entry		1	2	Time (h)	Yield[b] (%)
1	**a**	R = Bn		0.5	74
2	**b**	R = PMB		0.5	77
3	**c**	R = Me		0.5	74
4	**d**			1	85
5	**e**			0.5	86
6	**f**			0.5	86
7	**g**			0.5	84
8	**h**			0.5	86
9	**i**			2	52
10	**j**			2	57
11	**k**			1.5	71
12	**l**			1.5	72
13	**m**			1	80
14	**n**			2.5	52
15	**o**			24[c]	46

[a]Reaction conditions: **1** (1 equiv) and EDA (5 equiv) in CH_2Cl_2 [0.2 M], add $BF_3 \cdot OEt_2$ (1 equiv) at 0 °C, stirred at rt. [b]Isolated yield after column chromatography. [c]See text for details.

55% (entry 19). On the other hand, increasing the amount of EDA to 5.0 equiv improved the yield to 77% and allowed full consumption of **1a** (entry 20). We thus established that the optimal conditions were to use 5.0 equiv of EDA and 1.0 equiv of $BF_3 \cdot OEt_2$ at room temperature, at a concentration of 0.2 M in CH_2Cl_2.

We repeated the reaction on **1a** under optimized conditions and **2a** was isolated in a 74% yield (Table 2, entry 1). This represents an 18% improvement over the isolated yield obtained with unoptimized conditions (Table 1, entry 4). We then synthesized multiple aldehydes **1** bearing different substituents to see how it impacts reactivity.[15] Not surprisingly, the reaction tolerated various *N*-alkyl groups on the aniline including PMB and methyl groups. Both indoles **2b** and **2c** were prepared from their corresponding 2-aminobenzaldehyde **1b** and **1c** in 77% and 74% yield, respectively (entries 2 and 3). The reaction gives higher yields when the aromatic ring is electron deficient (entries 4−8). The method is also tolerant of bromine and iodine substituents (entries 5 and 6), both of which could be subsequently functionalized by using cross-coupling reactions for the generation of more diversified intermediates. It is important to note that all the reactions with electron-neutral and deficient benzaldehydes **1** were very rapid and completed within 30 min, except for the case of **1d** where the benzaldehyde is ortho disubstituted (60 min reaction time).

Performing the reaction with a more electron-rich benzaldehyde **1** gave lower yields (entry 9) and the reaction time was also much longer (2 h). The presence of meta and para alkyl groups had little influence on the reaction yields (entries 11 and 12) although ortho substitution did lead to a lower yield (entry 10).

The presence of another fused aromatic ring was tolerated since the reaction of the naphthalene derivative **1m** furnished **2m** in 80% yield (entry 13). The method is also suitable for the preparation of 7-azaindole derivative **2n**, which was obtained in 52% yield from the corresponding aldehyde **1n**. The lower yield in this case can again be attributed to the lower reactivity observed with electron-rich benzaldehydes. Finally, we tried the reaction with the acetophenone derivative **1o**, which furnished the desired 2,3-disubstituted indole **2o** in a still respectable 46% yield. The reaction time required was much longer for this substrate.[16]

In conclusion, we developed reaction conditions for the direct transformation of *N*-alkyl-2-aminobenzaldehyde to 3-ethoxycarbonylindoles. The reaction proceeds in moderate to good yields from readily available 2-(alkylamino)benzaldehyde. A wide variety of 4-, 5-, and 6-substituted indole cores can be synthesized under very mild conditions with this procedure. Further studies to extend the scope of this transformation to include disubstituted diazo as well as acetophenone derivatives are currently underway.

Experimental Section

General Procedure for the Synthesis of Indoles: Ethyl 1-Benzylindole-3-carboxylate (2a). To a solution of 2-(benzylamino)-benzaldehyde (**1a**) (100 mg, 0.47 mmol) and EDA (243 μL, 2.18 mmol) in DCM (2.4 mL) at 0 °C was added $BF_3 \cdot OEt_2$ (60 μL, 0.47 mmol) dropwise. The ice bath was removed upon completion

(15) Benzaldehydes **1** were readily prepared on gram scale from the corresponding anthranilic acids. See the Supporting Information for details.

(16) Further investigations revealed that the desired addition/1,2-aryl shift step occurred quite rapidly (less than 2 h), but the subsequent condensation was very long.

of the addition and the solution was stirred at room temperature for 30 min. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and it was extracted (3×) with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield an orange oil. The crude residue was purified by flash chromatography (10:1 hexanes:EtOAc) to afford 97 mg (74%) of compound **2a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.64 Hz, 1 H), 7.90 (s, 1 H), 7.37−7.24 (m, 6 H), 7.19 (d, J = 6.76 Hz, 2 H), 5.37 (s, 2 H), 4.53−4.36 (m, 2 H), 1.47 (t, J = 7.10 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 136.4, 135.6, 134.2, 128.6, 127.7, 126.6, 126.4, 122.5, 121.6, 121.4, 109.9, 107.5, 59.3, 50.3, 14.2. HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$ 280.1338, found 280.1344.

Acknowledgment. The author would like to thank Merck Frosst for financial support.

Supporting Information Available: Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.